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IN CONNECTION WITH DIPHTHERIA AND
CONDITIONS WITH WHICH IT HAS
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A RETROSPECTIVE view of the confusion of ideas that existed upon diphtheria prior to the discovery of its etiology illustrates how essential to a correct understanding of the manifold phases of a disease is a knowledge of its cause. From the time of Bretonneau to the date of the observations of Klebs and of Loeffler much valuable information was accumulated, but in the state of knowledge in existence at the time it could hardly be estimated at its true value.

It may be of profit to pass in review some of the more important features of the disease, and endeavor to learn in how far opinions expressed by the early observers have been supported or refuted by the results of later methods of investigation.

The first observations that attracted attention to the disease, diphtheria, as we know it, were made in

¹ Read at the meeting of the Pathological Society of Philadelphia, held Nov. 8, 1894.



1826, by Bretonneau, of Tours, who endeavored to extricate from the chaotic mass of ideas existing at the time some definite conception of a malady that had hitherto been loosely classed with a group of gangrenous and necrotic conditions with which it had but little in common, either clinically, anatomically or etiologically. He suggested the use of the term "diphtheritis" for the disease, which was characterized by the presence of a skin-like pellicle upon the mucous membrane of the throat, for the reason that he considered this the feature by which it was distinguishable from all others with which it might be confounded. It may be mentioned at this point that in 1771, Samuel Bard, of New York, in a monograph entitled *An Inquiry into the Nature, Cause and Cure of the Angina Suffocativa, etc.*, gave a description of the clinical and anatomic manifestations of diphtheria that was quite comparable, in its essential details, with that subsequently given by Bretonneau.

Though Bretonneau's teachings constituted a step in the right direction, and did much to relieve the confused notions upon the malady, it was not long before objections were raised to the grounds taken by him. The teachings of Home, from 1765, to the effect that there existed a disease, designated as croup, and characterized by the formation of pseudo-membranes in the larynx, were revived, and there was thenceforth a division of opinion, some adhering to the teaching of Bretonneau, viz., that all the pseudo-membranous processes in the upper air-passages were identical, while others, with Home, believed in the existence of two distinct

affections. With the hope of clearing away doubts and shedding some light upon the disputed point, the question was taken up by the pathologists, and through the labors of Virchow, Weigert, Cohnheim and their pupils, the two processes were subjected to histologic study. The outcome of this work was a classification based entirely upon anatomic grounds and a nomenclature that was used only in its anatomic sense. From this standpoint it was taught that there existed: 1st, a true croupous process, characterized by the deposition of a fibrinous pseudo-membrane upon the surface of the mucous membrane; 2d, that there existed a true diphtheria, similarly characterized by the local appearance of a fibrinous condition, which was not, however, confined to the surface of the mucous membrane, but extended into it; and 3d, that there existed a mixed anatomic condition known as diphtheric croup, in which there appeared both the superficial pseudo-membranous deposit and the involvement of the deeper underlying structures; this latter being the local condition commonly seen in true diphtheria. The entire process in all cases was seen to be a coagulation-necrosis, the direct effect of the causative irritant, a process characterized by a combination of cell-death and inflammation, the coagulation and fibrin-formation resulting from the contact between the inflammatory serous exudate and the fibrin-ferment supplied by the dead cells.

While this is the anatomic nature of the local process in diphtheria, and constitutes the condition known as diphtheric, it is, nevertheless, one that occurs as a result of the action of many irritating

agents ; and, while always present as the local manifestation of diphtheria, it is often seen in other parts of the body than the throat, and in conditions that are etiologically distinct from diphtheria.

It is easy to see, therefore, that the use of the terms diphtheric and croupous in their anatomic sense, regardless of the causes underlying them, may, and doubtless often does, give rise to confusion. Though of the utmost importance in elucidating the nature of the tissue-changes seen locally in laryngeal and pharyngeal pseudo-membranous inflammations, these observations afforded but little aid to the clinician in recognizing the nature of the various exudates *intra vitam*. He was still obliged to rely, as hitherto, upon the symptoms and the naked-eye appearances of the exudations ; and it was then, as now, the experience of every clinician that these features of the disease are far too variable to admit of a positive diagnosis in all cases.

The means afforded for the correct diagnosis of the nature of these conditions constitute the first and most important outcome of the discovery of the cause of diphtheria. With the demonstrations by Loeffler, that there existed in the diphtheric deposits in the throats of all persons sick of diphtheria a distinct species of microorganism that was not present in other anatomically similar exudates, that the organism could readily be recognized, isolated and cultivated, and that it possessed the power, when introduced into susceptible animals, of reproducing conditions anatomically identical with those occurring in man afflicted with the disease, grounds for confusion could no longer exist, and from that time

the question has been not so much with regard to the anatomic character of the local pathologic changes as to the presence or absence of the specific causative factor. If this agent is present, diphtheria exists; if it is absent, then the local conditions and constitutional manifestations must be attributed to some other cause, and the disease is not diphtheria.

Thus it soon became manifest that the dispute over the relation between diphtheria and so-called membranous croup was to be uncontestedly settled. By the bacteriologic and histologic study of the latter condition it has been found to be due to the activities of the same microorganism that is concerned in the production of diphtheria, and to present fundamentally the same histologic conditions that are found in the diphtheric exudate. I am aware that there are still individuals who adhere to the opinion that true, specific, fibrinous laryngitis occasionally occurs spontaneously; but, unfortunately for this view, it is usually supported by clinical evidence alone, and has rarely, if ever, been formulated from the results of bacteriologic study of the cases.

Still another local process characterized by fibrinous exudation has been shown by bacteriologic analysis to be etiologically identical with diphtheria. I refer to the affection of the mucous membrane of the nostrils known as membranous rhinitis, a condition that receives but little attention because of the mildness of its clinical course, but which, nevertheless, depends for its existence upon the activities of the same organism that is concerned in producing diphtheria. Because of their apparently innocent nature these cases are not considered as menacing

to the health of individuals with whom they come in contact, and are not, therefore, isolated or otherwise regarded as dangerous, and yet examples are not wanting to show that they are communicable from one person to another, and there is some evidence to prove that true diphtheria has been contracted from them.

Another important question upon which there has been a conspicuous divergence of opinion, and which was also answerable only through the light shed by modern methods of research, is as to the local or constitutional origin of diphtheria. The careful study of an enormous number of cases occurring in man, and produced experimentally in animals, has demonstrated that the disease is purely local in its origin, and that the pseudo-membranous processes in the throat, the secondary manifestations in the internal organs, and the clinical symptoms, are one and all the result of a soluble poison, produced by a microorganism that has its seat of primary invasion in the mucous membrane of the upper air-passages. It is important to note that the disease is not a septicemia, in the sense of being associated with a distribution throughout the body of the microorganisms causing it, but is strictly a toxemia primarily, though a septic condition may be engrafted upon the toxic one later in its course.

Even the tissues in the throat in which the diphtheria-bacilli are growing give evidence of the effect of the poison independently of the immediate presence of the bacteria by which it was produced. In sections through the pseudo-membranes one sees that the most superficial layers contain bacteria in

large numbers, among which the bacillus diphtheriae can easily be recognized by its peculiar morphology; beneath this one sees a feebly-stained layer rich in cells but containing little or no fibrin, and in this layer the Klebs-Loeffler bacillus is often the only organism present; and especially is this the case just above the still deeper densely-stained fibrin-layer. The layer next to the mucous membrane is rich in fibrin, but contains no bacilli, and as a rule, no bacilli are found in the underlying necrotic mucous membrane.

The Klebs-Loeffler bacilli, we see, not only do not invade the infected mucous membrane, but do not usually even penetrate through the entire thickness of the diphtheric pseudo-membrane. The picture presented suggests a conflict at long range, so to speak, the invaders being the bacteria whose weapons are the easily soluble poisons manufactured by them upon the surface of the affected part, and through the absorption of which the tissues undergo the peculiar metamorphosis seen in this disease. If our bacteriologic investigations are conducted further into the remote internal organs, there too, we find an absence of the specific microorganisms. This is true not only for the internal viscera generally, but likewise for those organs affected with the peculiar form of localized necrosis described by Oertel as so common in this malady.

It is not, however, unlikely that during the course of the disease a few scattered organisms may accidentally gain access to either the lymphatic or vascular circulation, and thus become deposited in remote organs, as they may also be carried thither

through the phagocytic activities of wandering leukocytes. The possibility of finding diphtheria-bacilli in the internal organs at autopsies upon individuals dead of the disease has recently been demonstrated by Frosch, Wright, and others; but nothing that we have learned from the study of the conditions occurring in the deeper tissues leads to the belief that they are in any way dependent upon the immediate presence of the specific bacilli.

The poisons produced by the bacilli at the seat of primary invasion, to the absorption of which, as has been said, the secondary manifestations and constitutional symptoms are due, are likewise produced by the bacilli when growing under artificial conditions of cultivation.

When isolated, free from the organisms by which it was manufactured, it is seen to be capable of causing in susceptible animals identically the same group of tissues-changes that are produced when the bacilli themselves are introduced. The interesting and important features in connection with it are its nature, being analogous chemically to the venom of serpents, and the potency of its poisonous properties, which exceeds in degree that of almost any other substance with which we are acquainted. Roux and Yersin present some idea of the intensity of its action ; they have estimated that 0.4 milligram of the dried poison is sufficient to kill eight guinea-pigs weighing each 400 grams, or two rabbits weighing each two kilograms, a degree of toxicity almost beyond the grasp of our imagination.

In 1888 Oertel directed attention to a group of pathologic conditions that he found in the internal

organs of individuals dead of diphtheria ; and more recently this subject has attracted additional attention through similar observations made by Welch and Flexner upon animals that had died of the experimental form of the disease. These changes consist of foci of a peculiar form of necrosis, varying in extent and scattered irregularly through the internal organs. They are characterized by nuclear fragmentation of the cells of the parts affected. The fragments into which the nuclei are seen to disintegrate are conspicuous for the readiness and intensity with which they become stained and for the manifold shapes which they are seen to assume, at times appearing as little else than dust-like particles strewn through the necrotic and hyaline area, or again as clusters of granules indicative of the location of the nucleus from which they originated ; again, all manner of irregular and bizarre shapes that may be likened to whetstones, crescents, balloons, clubs, dumb-bells, etc., will be seen. Frequently a nucleus will appear as if drawn out so that it may present a tail-like elongation, and again it may be pinched and distorted. In certain spots there may be almost an absence of stained cells and fragments, but it is usually possible to detect faint outlines of cells and more or less of a refractive, granular substance that gives the staining reaction of fibrin. In the investigations of Oertel and of Welch and Flexner these necrotic areas in greater or less extent have been detected in all the internal viscera, being particularly prominent in the lymphatic apparatus, in the liver, and in the spleen. To a limited extent the same process was also detected in the muscles of the

heart. While not strictly confined to the disease, diphtheria, this nuclear fragmentation is nevertheless always an accompaniment, and affords, by the rapidity with which it is produced, another illustration of the energy of action possessed by the poison producing it. It has been seen to occur in the internal organs of animals with all its characteristics in so short a time as thirty-eight hours after inoculation with small quantities of cultures of the bacillus diphtheriae.

Through similar methods of investigation a satisfactory understanding of the pseudo-membranous anginas of scarlatina and measles has also been reached. These processes are not, as has been supposed, of a diphtheric nature, etiologically speaking, though it is often impossible to distinguish them from diphtheria by the means ordinarily possessed by the clinician. When not complicated with diphtheria the local manifestations in these diseases are etiologically quite distinct. They are due, as a rule, to a streptococcus similar to and probably identical with that concerned in the production of erysipelas and phlegmonous forms of inflammation. A clearer understanding of the pathology of these conditions has recently been reached through the studies of Booker, who states that from the material examined it is safe to say that the local changes seen in the throats of patients with scarlet fever and measles are anatomically distinct from those seen in diphtheria, and that the anatomic alterations observed in the deeper structures of the body resulting from the scarlatinal virus, unlike those secondary to diphtheria, are accompanied by the immediate presence of streptococci, and are largely suppura-

tive in nature, appearing to be the direct outcome of the organisms associated with them.

From this imperfect review of the more important of the mooted questions in connection with diphtheria and allied pseudo-membranous inflammations of the upper air-passages, it is manifest that such doubts could only have existed as a result of incomplete acquaintance with the causes underlying the several processes; and with the exact means of differentiation that have been afforded by newer methods of investigation our conception of the nature of these processes, particularly of diphtheria, occupies a place on a par with that of tuberculosis, anthrax, and other infectious maladies from which so much of value has been learned. The discovery of the bacillus *diphtheriae* and the practical application of the knowledge gained by this discovery has shed a flood of light upon these processes that could not possibly have been obtained through any other channel of study.

As bacteriologic study of diphtheria and conditions with which it might be confused met with wider application certain irregularities were encountered. It was discovered that the causative factor, the genuine bacillus *diphtheriae*, was simulated in morphologic and biologic peculiarities by what was believed to be another organism which was distinguishable from it only by the absence of pathogenic properties. This latter organism was known as the pseudo-diphtheric bacillus, and was considered as distinct from the genuine diphtheric bacillus simply because of its inability to kill susceptible animals when inoculated into them subcu-

taneously. As this organism had been seen in conditions not believed to be diphtheria, as it had been seen in mild cases of a doubtful nature, and as it had been seen in genuine diphtheria in association with the true diphtheria-bacillus, it became necessary to determine its relation to the virulent bacillus *diphtheriae* before the value of the latter organism as an absolute means of diagnosis could be firmly established. The simplest way out of the difficulty was to consider them as in no way related, but as entirely distinct species, and this, in fact, is what was done.

It was, however, soon observed that the genuine, virulent diphtheria-bacillus was liable to fluctuate in the degree of its pathogenic properties, at times possessing these to such an extent that when inoculated into guinea-pigs death resulted in from thirty-six to forty-eight hours, while again the period of inoculation was much longer, often reaching five and six days, and in not a few cases organisms were obtained from undoubted cases of diphtheria that failed to give more than a temporary local reaction when inoculated into these animals. In many cases of diphtheria the two organisms have been seen to be simultaneously present, and in the observations of Roux and Yersin it was detected that as the disease advanced toward recovery the number of the less virulent and non-virulent forms became more numerous in proportion. Singular as it may seem, the only, or principal point of distinction between these two organisms, if distinct they are, was held to be the ability of the one and the inability of the other to cause the death of the inoculated animals,

and no attention whatever was paid to the nature of the local reaction that was caused by the organism that failed to kill. I have taken occasion to examine the condition of the tissues at the seat of inoculation in animals into which non-virulent forms of this organism had been introduced, and have found that, though the death of the animals did not follow the inoculations, locally, tissue-changes indistinguishable, save in degree, from those produced by the fully virulent forms were to be found; there was the same edema, though less in extent, the same hyaline condition of the muscle-fibers, the same fibrin-exudation and the same characteristic fragmentation of nuclei that one finds locally in the animals inoculated with the true, fully-virulent bacillus of diphtheria. This, I think, offers another argument in favor of the opinion already expressed elsewhere by Roux and Yersin, myself and others, that the diphtheric bacillus and the so-called pseudo-diphtheric bacillus are one and the same organism, the latter representing the former, whose virulent properties have become diminished.

It must not be inferred, from what has been said in regard to the gradual appearance of the attenuated forms of this organism with the establishment of convalescence, that when recovery is complete, the organisms are no longer virulent. Such a conception would not accord with the results of observations upon convalescents from diphtheria. The study of a large number of cases has demonstrated that with recovery many of the diphtheric bacilli in the throat not only do not lose their virulence and vitality, but retain both these proper-

ties for days and weeks, and it is often possible to isolate from the throats of convalescents from diphtheria virulent diphtheria-bacilli for as long as two and three weeks after all traces of the disease have disappeared, a point of inestimable importance in establishing rational prophylactic measures against the spread of the malady.

It is interesting that it is not always possible to establish a dependence between the clinical course of the disease and the degree of virulence possessed by the organisms causing it. From many of the most alarming cases organisms are often isolated that are much less virulent, as determined by their period of incubation in animals, than those seen in other cases, the clinical manifestations of which are much milder. There are undoubtedly modifying conditions at play, upon whose nature we can do little more than speculate—conditions, possibly, of individual susceptibility or tolerance to the action of the poison, or some local factor favors or retards the absorption of the poison from the point at which it is produced; certain it is that in its clinical, anatomic, and certain of its bacteriologic phases, diphtheria varies within very wide limits, but possesses at the same time certain features that serve to distinguish it from other diseases with which it is likely to be confounded.

With the further application of bacteriologic methods to the study of diphtheria, attention was turned to the question of immunity against the disease, and finally to the discovery of a cure.

The outcome of experiments conducted principally by Behring, Kitasato, Wernicke, Wasser-

mann, Brieger, Ehrlich, Roux, Martin, and others, is to apply to diphtheria the principles of the important observations made by Behring and Kitasato upon tetanus, to the effect that the blood-serum of animals that have been immunified against tetanus possesses not only the power of conferring immunity against this disease to animals into which it may be injected, but that it also possesses the property of arresting the malady after it is already in progress. This observation represents the foundation-work of blood-serum therapeutics, around which so much interest has lately centered.

Through the combined labors of those cited, and more especially through the investigations of Behring, it has been found possible to do in diphtheria just what he and Kitasato did in tetanus, viz., it is possible to render susceptible animals immune to diphtheria by the introduction into their tissues of the modified poisons produced by virulent diphtheria-bacilli, and to obtain from the blood of these animals serum that will not only afford immunity to other susceptible animals, but which, as in the case of tetanus, has the power of arresting the disease after it has already been in progress for a time. When this method of treatment is applied to animals that have purposely been infected with pure cultures of the bacillus diphtheriae, and not too long after infection, the results are so uniformly favorable as to place the operation far beyond the experimental stage. If, however, the disease is permitted to proceed for a time the results are not to be counted upon with such certainty; in short, the success of the operation is dependent upon the

stage to which the disease has progressed. In mixed infections, that is, those in which some other organisms, especially the streptococcus, commonly associated with the bacillus diphtheriae in human diphtheria are present, the experiments of Roux and Martin indicate that the results of the treatment are still less certainly favorable.

You are all too well acquainted with the astonishingly favorable statistics that have been presented recently for hospitals in which this method of treatment has been employed, to require mention of the reduction in the death-rate from diphtheria since the use of this method, and I believe it safe to predict that as our knowledge upon the subject increases, and as we become more familiar with some of the obscure points the results of the treatment will be still more favorable.

As to the *modus operandi* of the immunifying process and the therapeutic action of the serum of the immunified animals, we are still in the dark; but the hypothesis of Buchner, to the effect that the introduction into susceptible animals of the modified poisons produced by virulent bacteria serves as a stimulus to the integral cells of the tissues, and awakens a reactionary change that results in the appearance in the circulating blood of a something that is highly antagonistic to the fully toxic poisons that may subsequently gain access to these animals, seems most reasonable, and at present meets the requirements of the case more satisfactorily than any of the other explanations that have been advanced.

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